

REMARKS

The Present Invention and Pending Claims

Claims 24, 25, 27, 28, 30, 33, and 35-42 are currently pending and directed to a creatine amidinohydrolase (claims 24, 25, 27, 28, 30, 33, and 35-37), a method for producing creatine amidinohydrolase (claim 38), a reagent for determination of creatine in a sample (claims 39 and 41), and a method for determining creatine in a sample (claims 40 and 42).

Amendments to the Specification and Abstract

The specification and abstract have been amended to correct a typographical error. Specifically, the specification and abstract have been amended to recite an isoelectric point (pI) of about 4.5. The amendments to the specification and abstract are supported by the specification as originally filed because the correct pI value is intrinsic to the creatine amidinohydrolase encoded by the nucleic acid sequence of SEQ ID NO:2, which encodes the amino acid sequence of SEQ ID NO:1, of which the specification enables the isolation and characterization. Specifically, the disclosure enables the isolation of the creatine amidinohydrolase gene of SEQ ID NO:2 from *Alcaligenes faecalis* TE3581 (FERM P-14237) which encodes amino acid of SEQ ID NO:1 (see, e.g., column 4, lines 5-14). Accordingly, no new matter has been added by way of these amendments.

Amendments to the Claims

Claims 24, 25, 27, 33, and 35-37 have been amended to point out more particularly and claim more distinctly the present invention. Specifically, claims 24 and 25 have been amended to incorporate the characteristics of claims 27 and 29, respectively. Accordingly, claim 27 has been amended and claim 29 has been canceled to prevent redundancy.

Additionally, claims 26, 31, 32, and 34 have been cancelled. Claims 25 and 27 have been amended to recite the temperature at the optimal pH as supported by the specification at, for example, column 7, lines 12-19. Claims 24, 33, and 35-37 have been amended to recite the pH at the optimal temperature as supported by the specification at, for example, column 7, lines 1-24. Claims 24, 25, 33, and 35-37 have been amended to recite an isoelectric point of about 4.5, which is supported by the specification and abstract as discussed above. No new matter has been added by way of these amendments.

Request for Personal Interview

Applicants respectfully request a personal interview with the Examiner to discuss the outstanding issues and this response to the Office Action dated November 1, 2002. Please contact the applicant's attorney, John Kilyk, Jr., to arrange an interview date.

The Office Action

The Office has rejected claims 24-42 under 35 U.S.C. § 112, first paragraph, as containing subject matter that allegedly was not described in the specification in such a way as to reasonably convey that the inventors had possession of the claimed invention at the time the patent application was filed, and for alleged lack of enablement. The Office has rejected claims 27, 29, 31, and 33-37 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claims 24 and 28 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Japanese Patent Application Number 62-099182. Reconsideration of these rejections is hereby requested.

Discussion of the Rejection under 35 U.S.C. § 112, first paragraph

The Office has rejected claims 24-42 under Section 112, first paragraph, as containing subject matter that allegedly was not described in the specification in such a way as to reasonably convey that the inventors had possession of the claimed invention at the time the patent application was filed. Additionally, the Office contends that the specification does not provide enablement for the subject matter of claims 24-42. Applicants traverse these rejections for the following reasons.

The Office contends that claims 33 and 35-37 contain new matter due to the recitation of optimum temperature at “a pH of about 6-8.” The Office contends that a temperature optimum was only measured at pH 7.5 and, therefore, that there is no indication that optimum temperature was sustained within the range of pH 6-8. Claims 33 and 35-37 (as well as claims 24 and 27) have been amended to recite a temperature optimum at a pH of about 7.5. Accordingly, this written description rejection is believed to be moot.

The Office contends that claims 24-42 lack written description because the claims recite a preamble which does not limit the number of mutations, such that the preamble is not considered a limitation. Moreover, the Office contends that claims 24-42 are not enabling for a creatine amidinohydrolase having the wide range of enzymes encompassed by the claims. The pending claims, as amended, recite numerous physiochemical properties (including an isoelectric point of about 4.5) that specifically define the creatine amidinohydrolase of present invention.

The isoelectric point (pI) value of 3.5, as recited in the original specification and claims, was a typographical error, and therefore the value is amended by way of the specification and claim amendments recited herein. The correct pI value of about 4.5 is supported by the specification as originally filed because the correct pI value is intrinsic to the creatine amidinohydrolase encoded by the nucleic acid sequence of SEQ ID NO:2, which encodes the amino acid sequence of SEQ ID NO:1, of which the specification enables the

isolation and characterization. Specifically, the disclosure enables the isolation of the creatine amidinohydrolase gene of SEQ ID NO:2 from *Alcaligenes faecalis* TE3581 (FERM P-14237) which encodes amino acid of SEQ ID NO:1 (see, e.g., column 4, lines 5-14). Correction of a physiochemical property that is intrinsic to the creatine amidinohydrolase described in the specification as originally filed does not add new matter (see, e.g., MPEP 2163.07).

As discussed in the previous Office Action, the pI value refers to the pH of a solution at which the total charges of an amphoteric electrolyte becomes 0 (i.e., neutral). The twenty different amino acids, which make up proteins, are amphoteric electrolytes having positive charges (e.g., amino group) or negative charges (e.g., carboxyl group). Each amino acid has a specific pI value. Accordingly, a protein composed of amino acids is an amphoteric electrolyte having a pI value unambiguously determinable from the amino acid sequence of the protein.

The pI value as recited in the disclosure and original claims of the underlying patent was directly determined from test measurements. The measurements from such tests inevitably result in a range of values (\pm a few percent), even when the test operation is completed appropriately with no mistakes. This means that the pI value in the issued claims of the underlying patent inherently included a certain variation (even putting aside the fact that the actual numerical value is a typographical error), as is true with any other pI value, which is why the underlying patent included the term "ca." ("circa" which means "about") before the isoelectric point value.

The amended claims recite the same number and type of physiochemical properties recited in the original claims, as well as an additional characteristic related to the sequence of the creatine amidinohydrolase of the present invention. Specifically, the amended claims recite a creatine amidinohydrolase encoded by a nucleic acid sequence obtained by mutation of (a) the nucleic acid sequence of SEQ ID NO:2 or (b) a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:1. Given the total number of the amino acids of the creatine amidinohydrolase that represents the source material recited in the pending claims (i.e., 404 amino acids), the difference in the amino acid sequence between the source material and mutants, or between different mutants, is expected to be 2-3% at most, so as to preserve the inherent function and recited physiochemical properties of the enzyme, including an isoelectric point of about 4.5. For example, applicants submitted in the previous Office Action the pI values of several of the mutants described in the specification, which have the claimed characteristics. Such mutants had very minimal mutations in the amino acid sequence of SEQ ID NO:1 (e.g., only the 135th Arg has been substituted by Ala in the mutant corresponding to pCRH273M1 (as described in the specification at column 9, lines 34-39)).

Thus, the amended claims recite the numerous physiochemical properties that were present in the original claims (e.g., isoelectric point, optimum temperature and pH, molecular weight), and furthermore recite that the creatine amidinohydrolase is encoded by a nucleic acid sequence obtained by mutation of (a) the nucleic acid sequence of SEQ ID NO:2, or (b) a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:1. The recitation of these characteristics clearly defines the creatine aminidohydrolase of the present invention, such that the number of mutations encompassed by the pending claims is sufficiently limited. Moreover, as discussed above, the specification describes several examples of creatine amidinohydrolases which meet the characteristics of the claims, for example, the specification describes mutants corresponding to pCRH273M1 (see, e.g., column 9, lines 34-39), pCRH273M2 (see, e.g., column 9, lines 34-39), and pCRH273M3 (see, e.g., column 9, lines 34-39).

For the above reasons, the pending claims are clearly defined, as well as enabled by the specification. Specifically, the pending claims, as amended, clearly define a creatine amidinohydrolase by several physiochemical properties, including pI value and sequence, such that one of ordinary skill in the art would have recognized that the inventors had possession of the claimed invention at the time the patent application was filed.

For the foregoing reasons, the rejections under Section 112, first paragraph, should be withdrawn.

Discussion of the Rejection under 35 U.S.C. § 112, second paragraph

The Office has rejected claims 27, 29, 31, and 33-37 under Section 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

The Office contends that the term "pH stability" is unclear because the amount of activity required to be stable is not defined. Moreover, the Office contends that the phrase "not more than about 50 °C" in relation to "heat stability" is confusing, because the activity of the enzyme is not defined and the range is open-ended.

Claims 29, 31, and 34 have been cancelled. Claims 33 and 35-37 (as well as claims 24 and 25), as amended, no longer recite pH stability or heat stability. Additionally, claim 27 (as well as claim 25) has been amended to recite the temperature at the optimal pH. As such, the indefiniteness rejection is believed to be moot.

Discussion of the Rejection under 35 U.S.C. § 102(b)

The Office has rejected claims 24 and 28 under Section 102(b) as allegedly anticipated by Japanese Patent Application Number 62-099182. The pending claims, as amended, recite a

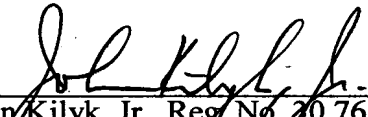
In re Appln. of Sogabe et al.
• Application No. 09/941,940

creatine amidinohydrolase encoded by a nucleic acid sequence obtained by mutation of (a) the nucleic acid sequence of SEQ ID NO:2 or (b) a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:1 with an isoelectric point of about 4.5. JP 62-099182 does not disclose a creatine amidinohydrolase with these characteristics. In that JP 62-099182 does not teach or suggest every element of claim 24 or 28, JP 62 099182 does not anticipate claim 24 or 28, and the Section 102 rejection should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



John Kilyk, Jr., Reg. No. 20,763
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson
Chicago, Illinois 60601-6780
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

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